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A SIMPLE AND INEXPENSIVE PROCEDURE FOR CHLOROMETHYLATION OF CERTAIN AROMATIC COMPOUNDS

Alexander McKillop,* Fereidon Abbasi Madjdabadi
and David A. Long

School of Chemical Sciences, University of East Anglia,
Norwich, NR4 7TJ, England.

ABSTRACT Reaction of a range of aromatic compounds with methoxyacetyl chloride and aluminium chloride in either nitromethane or carbon disulphide results in chloromethylation in good to excellent yield.

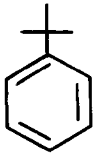
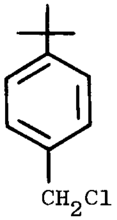
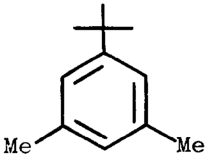
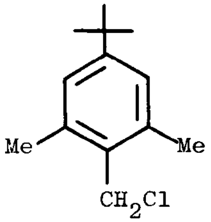
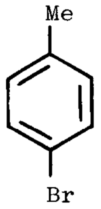
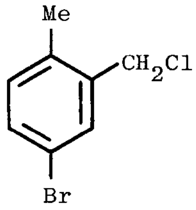
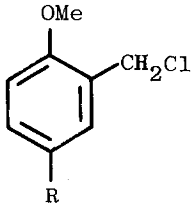
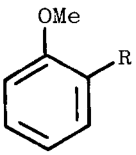
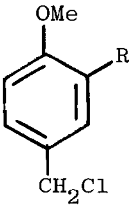
Chloromethylation of aromatic compounds was a very widely used reaction for well over half a century, both on a laboratory and industrial scale, until the hazards associated with chloromethyl and dichloromethyl ether (or reagent combinations which could result in the formation of these ethers) were recognised.[1,2] These hazards are apparently so severe that classical procedures for the direct chloromethylation of aromatic compounds under Friedel-Crafts are essentially no longer used, and other methods are employed for the synthesis of benzyl chlorides. Attempts have been made to develop alternative procedures for chloromethylation which do not utilise especially hazardous materials, but with no real success.[3]

We now describe a very simple process for chloromethylation of certain aromatic compounds which consists of reaction of the aromatic compound with methoxyacetyl chloride and aluminium chloride in either nitromethane or carbon disulphide, i.e. standard Friedel-Crafts conditions. Data for a variety of substrates are listed in Table I, and reveal that the procedure is especially effective for anisoles (and presumably other aryl ethers) which contain a powerful electron withdrawing group in the ortho or para position.

In general, the present procedure is similar to classical chloromethylation with respect to the effects of substituent groups, and formation of diarylmethanes becomes the predominant reaction as the aromatic substrates

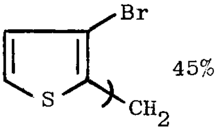
TABLE I

Chloromethylation of Aromatic Compounds using $CH_3OCH_2COCl/AlCl_3$

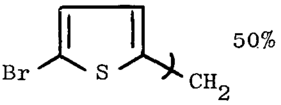
Aromatic Compound	Product	Yield, %[a]
		80
		75[b]
		75
		R = CHO 70 = COMe 99 = COOMe 86 = CN 90 = NO_2 89
		R = CHO 90 = COMe 50 = COOMe 47

[a] Refers to pure, recrystallised or redistilled material. [b] Accompanied by 8.5% of di-(2,6-dimethyl-4-*t*-butylphenyl)methane.

become increasingly electron rich. 2- and 3-Bromothiophene, for example, give the diheteroarylmethanes 1 and 2 respectively in moderate yield. There

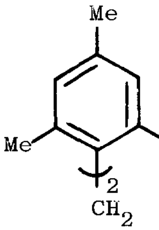


1



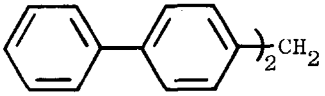
2

are, however, some noticeable differences. Thus, while mesitylene, biphenyl, p-bromoanisole and p-chlorotoluene can be readily mono- or dichloromethylated using classical techniques,[1,2] application of the present procedure gives only trace amounts of chloromethylated products; instead, the diarylmethanes 3 - 6 are obtained in good to excellent yield. Reactions of simple monosubstituted



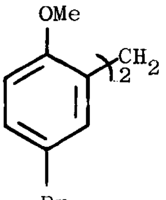
3

90%



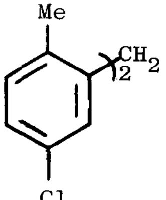
4

74%



5

70%

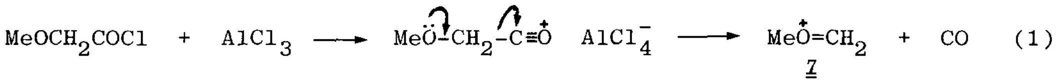


6

62%

aromatic compounds such as toluene and anisole with methoxyacetyl chloride/ aluminium chloride are of no synthetic utility: both chloromethylation and diarylmethane formation occur ortho and/or para to the activating substituents, and mixtures of products are obtained.

We have no unambiguous evidence on the mechanism of the present chloromethylation reaction. The synthetic approach was based on the assumption that methoxyacetyl chloride would react with aluminium chloride as shown in equation (1) to generate the methoxymethyl cation 7, and, indeed, carbon monoxide is evolved fairly rapidly when the two components are mixed. Reaction of the aromatic substrate with 7 would give a benzyl methyl ether, subsequent



$$\mathrm{MeOCH_2COCl} + \mathrm{AlCl_3} \longrightarrow \mathrm{Me\ddot{O}{-}CH_2{-}\overset{+}{C}{\equiv}O}\ \ \mathrm{AlCl_4^-} \longrightarrow \underset{\mathbf{7}}{\mathrm{Me\overset{+}{O}{=}CH_2}} + \mathrm{CO} \qquad (1)$$

complexation of which with aluminium chloride and displacement of the methoxy group by either chloride ion or a second molecule of aromatic substrate would lead to the observed products. It is interesting that in contrast to the Mannich reaction, there has been little detailed study of the solution chemistry of 7. There have been a number of ion cyclotron resonance studies and it has been emphasised recently that "more is now known of the chemistry of this ion in the gas phase than in condensed phase".[4,5] We have not, however, been able so far to demonstrate that 7 is the reactive intermediate in the substitution rather than, say, chloromethyl methyl ether formed by reactio of 7 with chloride ion. Further studies are currently in progress.

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References

1. R.C. Fuson and C.H. McKeever, Org. Reactions, 1, 63 (1942).
2. G.A. Olah and W.S. Tolgyesi, "Friedel-Crafts and Related Reactions", G.A. Olah, ed., Interscience Publishers, New York, 1963, Vol. 2, pp. 659-784.
3. G.A. Olah and M.R. Bruce, J. Am. Chem. Soc., 101, 4765 (1979).
4. M.C. Caserio and J.K. Kim, J. Org. Chem., 47, 2940 (1982) and references therein.
5. Reaction of methoxyacetyl chloride with HF/SbF_5 has been shown to give $Me\overset{+}{O}{=}CH_2.SbF_6^-$ which reacts with benzene to give toluene in high yield (G.A. Olah and J.J. Svoboda, Synthesis, 52 (1973)).

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